Toxic epidermal necrolysis in Stevens—Johnson syndrome

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Three cases are described in which Stevens–Johnson syndrome progressed in the course of a few days to toxic epidermal necrolysis. Trimethoprim–sulfamethoxazole, allopurinol in combination with hydrochlorothiazide, phenytoin and possibly ampicillin were implicated in the causation of the disease.

On décrit trois cas où un syndrome de Stevens–Johnson a évolué en l'espace de quelques jours vers une nécrolyse épidermique. Le triméthoprim–sulfaméthoxazole, l'allopurinol en association avec l'hydrochlorothiazide, la phénytoïne et, possiblement, l'ampicilline ont été impliqués comme facteurs étiologiques de la maladie.

Toxic epidermal necrolysis is a serious, devastating skin disease with a high mortality and multiple etiologic factors. The purpose of this communication is to report three cases of toxic epidermal necrolysis due to drugs that are commonly used by physicians, to illustrate important points in management and to support the view that drug-induced toxic epidermal necrolysis is a severe form of Stevens–Johnson syndrome.

Case reports

Case 1

A generalized skin eruption, fever and malaise developed in a 43-year-old woman over a period of 72 hours. Previously she had been in excellent health and had taken no medication systemically except trimethoprim–sulfamethoxazole for 2 weeks because of otitis media.

She was acutely ill and had erythematous papules and plaques on the limbs and trunk, and target lesions with overlying bullae. On the back the bullae tended to coalesce into large desquamated sheets. Similar involvement was seen around her eyes and mouth, and her oropharyngeal and laryngeal mucous membranes showed extensive ulceration.

She was admitted to hospital, placed in "reverse isolation" and given intravenous fluids and hydrocortisone. A skin biopsy specimen showed subepidermal bulla formation with complete necrosis of the epidermis and minimal perivascular infiltration of lymphocytes in the dermis. The initial bullous erythema multiforme worsened, with development of massive flaccid bullae and desquamation of skin in large sheets. By the 5th day of hospitalization she could tolerate a soft diet and her drug therapy was changed to prednisone, given orally. She was discharged after 3 weeks with residual postinflammatory pigmentation and complete loss of the nail plate of most of her fingers.

Case 2

A 38-year-old man was admitted to hospital with a generalized bullous skin eruption and severe involvement of his oral and conjunctival mucous membranes. He had been well until 5 days prior to admission, when, while he was vacationing in Mexico, an erythematous, macular, burning rash developed, mainly on his shoulders and around his neck. It quickly spread to involve most of the skin surface but spared the bathing trunk area. He was given corticosteroids intravenously and orally in undetermined amounts but thought he was getting worse and returned to Canada, going directly to the hospital's emergency department. Previous medications were hydrochlorothiazide, 50 mg/d for 2 years for essential hypertension, and allopurinol, 200 mg *tid* for 6 weeks prior to admission following four attacks of gout.

He was acutely ill, with a temperature of 40.6°C and a pulse rate of 110 beats/min. The widespread bullous skin eruption was composed of erythematous macules and confluent areas of erythema surmounted by bullae. Target lesions were present. Over the back the bullae tended to coalesce. He also had severe ulceration of his buccal mucosa and crusted hemorrhagic ulcers on his lips (Fig. 1), as well as severe ulcerative conjunctivitis (Fig. 2). A diagnosis of severe Stevens–Johnson syndrome was made and over the next 2 days the skin on the back and upper arms began to desquamate in large sheets (Fig. 3).

Three biopsy specimens from different areas of skin showed complete necrosis of the epidermis with separation at the dermoepidermal junction and a minimal perivascular lymphocytic infiltrate.

Treatment consisted of prednisone, 80 mg/d given orally, Burow's compresses and silver sulfadiazine cream applied to all skin surfaces. Cultures from skin, throat and nose, as well as of three blood samples taken at the time of admission,

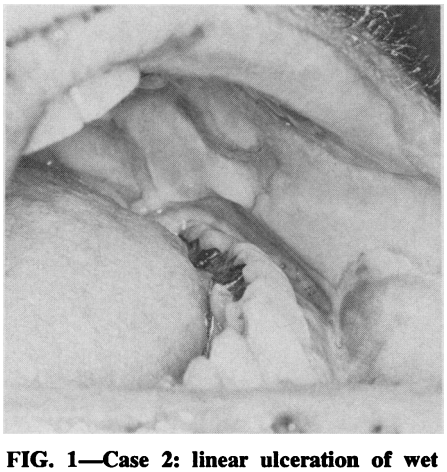

FIG. 1—Case 2: linear ulceration of wet labial mucosa and extensive buccal involvement.

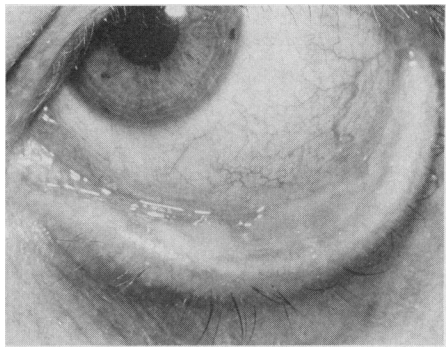

FIG. 2—Case 2: extensive ulceration of conjunctiva.

FIG. 3—Case 2: fine wrinkling and denudation on back.

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were negative. Within 3 weeks the rash cleared completely, leaving pronounced erythema of the back and face, and he was discharged taking 45 mg/d of prednisone orally, the daily dose to be decreased gradually.

Case 3

A 71-year-old woman was admitted to hospital through the emergency department in a coma. A diagnosis of subarachnoid hemorrhage was made and angiograms showed an aneurysm of the basilar artery. In the neurosurgical intensive care unit she was treated with dexamethasone and phenytoin but failed to regain consciousness.

Two weeks after admission she was given a 10-day course of ampicillin because of a urinary tract infection. Three days after cessation of therapy a widespread maculopapular eruption (Fig. 4) and a fever of 38.5°C developed. The rash involved mainly the face, trunk, arms and, to a lesser extent, the thighs and legs. There was crusting on her lips and nasolabial folds. Most of the lesions of the trunk were confluent and there were a few target lesions. She also had periorbital swelling.

She was thought to have erythema multiforme secondary to therapy with either ampicillin or phenytoin, so the latter was discontinued. Over the next few days large flaccid bullae developed and sheets of skin over the trunk, axillary folds and forehead began to exfoliate. A clinical diagnosis of toxic epidermal necrolysis was confirmed when a frozen section of a skin biopsy specimen showed complete necrosis of the epidermis (Fig. 5) and minimal perivascular infiltration of the dermis by lymphocytes. Despite systemic administration of steroids and application of Burow's compresses to the denuded skin, her condition deteriorated rapidly and she died 5 days after onset of the skin lesions.

Discussion

In 1956 Lyell[1] described an entity occurring in older children and adults that he thought was similar to Ritter's disease of the newborn; he referred to it as "a toxic epidermal necrolysis, an eruption resembling scalding of the skin". The same year, Lang and Walker[2] described the same disease as "an unusual bullous eruption". The disease has since been called toxic epidermal necrolysis, Lyell's syndrome and scalded skin syndrome. Over the years further studies by Lyell and colleagues[3-6] and by others[7,8] led to the differentiation of two groups of diseases.

One group of diseases usually occurs in children less than 10 years of age. The skin suddenly reddens and peels; it is usually tender and can be stripped off by very light pressure, leaving a shiny red, oozing surface. Biopsy specimens show partial necrosis of the epithelium, with separation in the upper malpighian layers. Extensive denudation occurs, often with ulceration of the conjunctiva and fissuring of the lips. The buccal mucosa is not extensively involved. In a high percentage of cases, *Staphylococcus aureus* can be found either on the skin or as a focal infection elsewhere in the body. It was not until 1970 that Melish and Glasgow[9,10] created an animal model of the disease and identified an epidermolytic toxin produced by *S. aureus* group 2, phage type 71. Prompt treatment leads to gratifying recovery; the mortality is approximately 5%.[11]

A second group of diseases can be identified clinically and pathologically. A variety of drugs have been implicated as inducing the symptom complex, and a number of reviews, notably those of Lyell,[3] Bianchine and associates[12] and Böttinger, Strandberg and Westerholm,[13] have discussed the likelihood of drug association. Over half the cases reported since 1956 have occurred in conjunction with drug ingestion. The most common drugs associated are sulfonamides, particularly long-acting ones, penicillin and other antibiotics, phenylbutazone and other pyrazolone derivatives, anticonvulsants[14] and barbiturates. Recently allopurinol has been suggested in several reports as a causative factor.[15-18] Most eruptions occurred 1 month after treatment began in patients who were taking thiazide diuretics concomitantly.

We agree with Lyell's subsequent statement that drug-induced toxic epidermal necrolysis is a severe form of Stevens–Johnson syndrome.[19] This syndrome may occur after a viral infection, be drug-induced or, most commonly, be of unknown cause. Synonyms include erythema exudativium multiforme, ectodermosis erosiva periorificialis and erythema multiforme major. Other investigators[20-22] have also supported this view.

Erythema multiforme is a character-

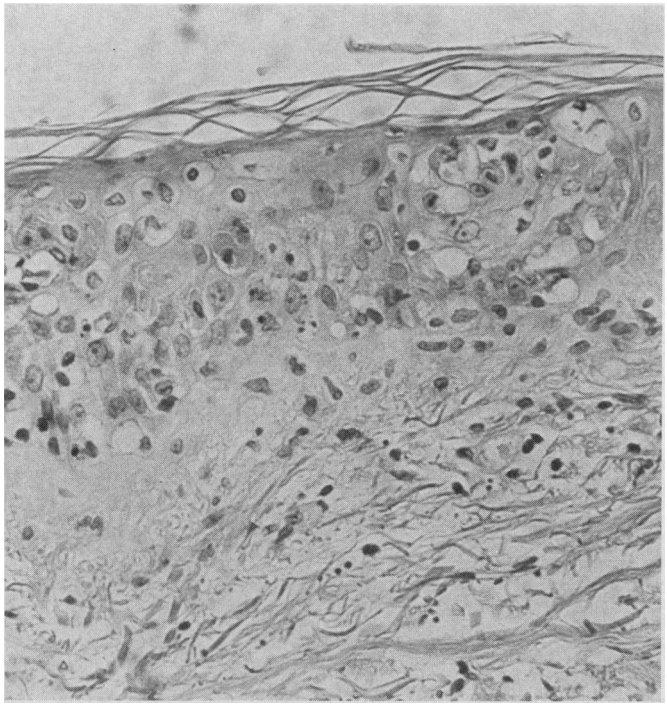

FIG. 4.—Case 3: biopsy specimen from early lesion, showing focal spongiosis and occasional epidermal cell necrosis. Lack of dermal inflammation (hematoxylin–eosin; original magnification, ×250, reduced by 20%).

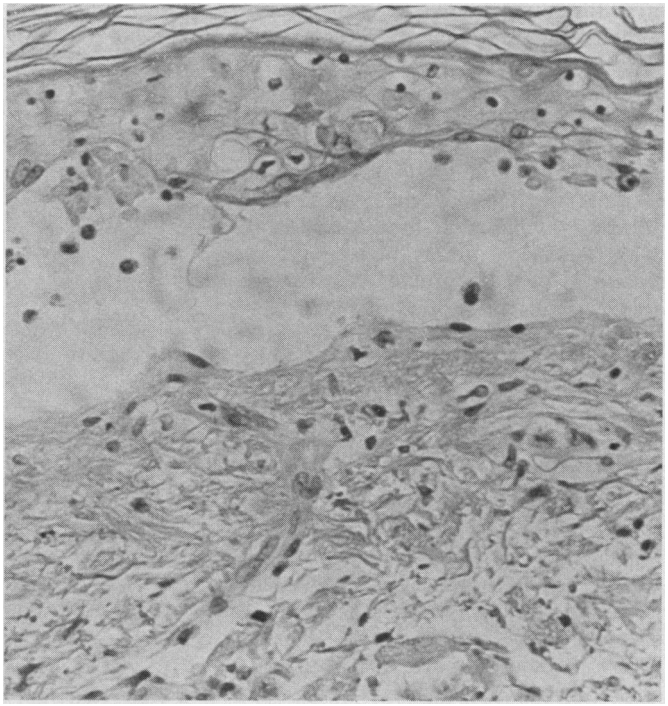

FIG. 5—Case 3: biopsy specimen from wrinkled skin, showing complete necrosis of epidermis with separation at dermoepidermal junction (hematoxylin–eosin; original magnification, ×250, reduced by 20%).

istic reaction pattern of the skin, with the sudden onset of round, macular, erythematous lesions in which a central bulla or necrosis develops over a few days. The periphery of the lesion may advance in concentric rings, producing the classical iris or target lesion. The eruption may be generalized and often affects the palms and soles. Punched-out oral and genital ulcerations may be present. The condition is idiopathic in many cases but *Mycoplasma*, herpesvirus and drugs are among a long list of possible causative agents. The same skin lesions may occur in Stevens–Johnson syndrome, but here severe ulceration of conjunctiva, oral mucosa and nasopharynx and larynx is the rule, and systemic symptoms (including fever and malaise) are more severe.

A biopsy specimen from a flat, macular lesion of erythema multiforme will show a perivascular lymphocytic infiltrate, dermal edema and a few lymphocytes migrating into the epithelium. A bullous lesion of erythema multiforme will show spongiosis (edema) of the epithelium and a subepidermal bulla in addition to the previously described findings. In contrast, the skin lesions in Stevens–Johnson syndrome will show total epidermal necrosis, separation of the dead epithelium from the dermis, and only a light dermal infiltrate. These findings are also seen in toxic epidermal necrolysis of the drug-induced type.

Cases 1 and 2 were typical in the histologic findings. Early lesions may not show such severe changes and, in fact, the early lesions in case 3 were compatible with macular erythema multiforme and only focal necrosis of individual cells in the epithelium was noted. The flaccid bullae that developed later, however, showed total necrosis of the epithelium and the superficial portions of the sweat ducts. Obviously with such total necrosis re-epithelialization takes longer and the patient is at a far greater risk for secondary bacterial infection. This is in contrast to the staphylococcal scalded skin syndrome, in which necrosis occurs in only the superficial layers of the epithelium.

The onset of epidermal necrolysis in Stevens–Johnson syndrome is clinically different from the onset of staphylococcal scalded skin syndrome. In the former there is fever, malaise and the appearance of small, macular, well demarcated lesions. Target lesions are often present initially. There is more severe involvement of the oral mucosa, especially the buccal mucosa and the wet portion of the labial mucosa. Conjunctival involvement is extensive.

Although tense blisters up to 1 cm in diameter are seen in erythema multiforme, the blisters in toxic epidermal necrolysis are much larger and flaccid. In some areas a wrinkled epithelium is noted surmounting the erythema, and bullae are not formed. Such epithelium peels off with minimal pressure. The wrinkling becomes more severe over a 48-hour period and the lesions become confluent, especially on the back and face. In staphylococcal scalded skin syndrome, peeling and denudation are much more rapid, occurring within a few hours of onset of the illness.

In view of the complete loss of the epidermal barrier over large areas of the skin in drug-induced toxic epidermal necrolysis, fluid and electrolyte loss as well as sepsis are common complications. The mortality is 25% to 30%.

Optimum management of toxic epidermal necrolysis in Stevens–Johnson syndrome includes reverse isolation, application of compresses to prevent excess blister fluid pushing off sheets of epithelium, and occlusion with silver sulfadiazine cream. Gentle nursing care is essential and regular cultures of any purulent areas are mandatory. The inciting cause must be removed. The literature is conflicting as to whether systemic administration of steroids is helpful; it is not indicated in staphylococcal toxic epidermal necrolysis,[23] but in drug-induced toxic epidermal necrolysis it seems to prevent the development of further lesions. Our third patient appeared to die of septicemia complicating her neurologic condition. She did not receive aggressive steroid therapy and was not treated with reverse isolation or silver sulfadiazine.

In a patient with erythema multiforme-like skin lesions, severe involvement of conjunctiva and oral mucosa, fever and fine wrinkling of the skin over the lesions, progression to toxic epidermal necrolysis is likely. Examination of a frozen section[24] of a skin biopsy specimen taken from the area of wrinkling will confirm the diagnosis of full-thickness epidermal necrosis. Therapeutic measures should be instituted rapidly; one should not wait until marked denudation occurs.

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